

THE BRITISH JOURNAL OF DERMATOLOGY

APRIL 1960

SERUM CHOLESTEROL, URIC ACID AND PROTEINS IN PSORIASIS.

A. TICKNER AND P. D. MIER.

Institute of Dermatology, St. John's Hospital for Diseases of the Skin,
Homerton Grove, London, E.9.

A REVIEW of the serum cholesterol and uric acid levels of those patients of this hospital in whom they were requested revealed that a substantial minority of psoriatic patients showed a rise in one or other of these values. cursory examination of the literature was enough to tell us that similar findings had frequently been reported and had frequently been denied. It was of course possible that the serum cholesterol and uric acid estimations would only be requested where some abnormality of these was suspected. We therefore decided to carry out these investigations on all patients with psoriasis attending this hospital. The serum proteins and their fractions derived by paper electrophoresis were also measured.

INVESTIGATION.

All of the subjects were in- or out-patients of St. John's Hospital. As far as was possible, tests were carried out on a consecutive series of patients and it is considered that a representative cross-section of all sufferers from psoriasis was studied.

A total of 86 patients was investigated of which 44 were female and 42 male. The age distribution is shown in Table I.

TABLE I.—*Age Incidence of Cases.*

Age group (years).	% incidence.
11-20	6.7
21-30	18.7
31-40	12.0
41-50	21.3
51-60	22.7
61-70	16.0
71-80	2.6

The extent of the disease was slight in 32%, moderate in 29% and widespread in 39%. In 13% the condition of the skin was improving, in 46% it was static and in 41% it was worsening.

Methods.

Serum cholesterol was measured by the method of Sackett (1925), serum uric acid by the method of Brown (1945) and serum proteins as described by Tickner, McCabe and Mier (1959).

RESULTS.

Serum cholesterol :

The serum cholesterol was raised above 250 mg.% in 19.8% of cases. As shown in Tables II and III, the serum cholesterol is related to the extent but not to the progress of the disease and the unexpected finding has been made that the serum cholesterol is higher in cases of psoriasis with only a few lesions than in those with widespread disease. However, no statistical difference is apparent between cases of psoriasis which are getting better and those getting worse.

TABLE II.—*Relationship of Serum Cholesterol to Extent of Psoriasis.*

	Extent of disease.		
	Slight.	Moderate.	Widespread.
Mean values mg. %	234 (i)	215	198 (ii)
S.D. of mean	9.8	9.2	8.1
% cases having value—			
> 250 mg. %	32	17	10
< 150 mg. %	0	4	19

The difference between (i) and (ii) is significant, $P < 0.01$.

TABLE III.—*Relationship of Serum Cholesterol to Progress of Disease.*

	Progress of disease.		
	Improving.	Static.	Worsening.
Mean values mg. %	229	213	215
S.D. of mean	15	6.3	10
% cases having values—			
> 250 mg. %	30	19	19
< 150 mg. %	0	3	19

Differences not significant.

Serum proteins.—The abnormalities observed in serum proteins in psoriasis are summarized in Fig. 1.

In this figure the heights of the cross-hatched columns represent the mean values in patients with psoriasis, while the heights of the plain columns represent the mean values of a series of serum proteins of 27 normal individuals studied by us. The numbers underneath refer respectively to M , the mean value of a

particular fraction in psoriasis in g.%; S , the standard deviation of the observed values about the mean, and P , the probability that the differences observed between psoriatics and normals were due to chance. An asterisk at the top of the column denotes significant differences ($P < 0.05$).

The total proteins and albumin in the whole series of psoriatics was significantly lowered and the α_2 and β -globulins significantly raised.

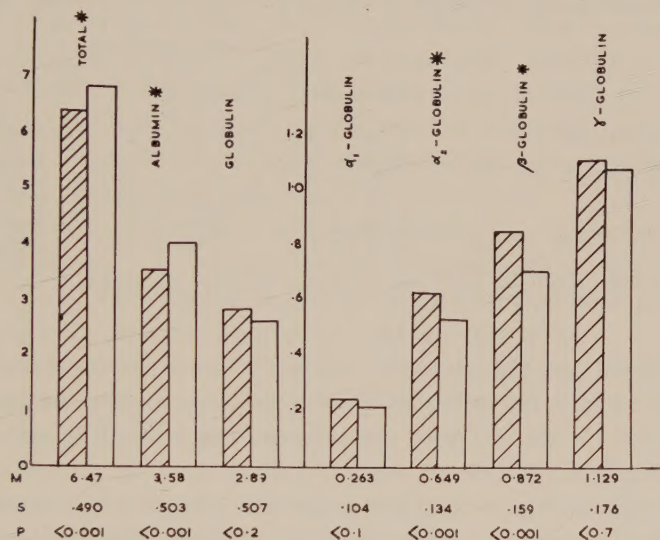


FIG. 1.

Table IV shows the relationship between serum proteins and the extent of the disease. The total protein and the albumin are lower the more widespread the disease.

It is probable that the levels of the globulin fractions vary with the extent of the disease, but a considerably larger series than the present one would be necessary to demonstrate this incontrovertibly. The trend, however, is for

TABLE IV.—Relationship of Serum Proteins to Extent of Disease (figures—g.%).

	Extent of disease.		
	Slight (a).	Moderate (b).	Widespread (c)
1. Total proteins . . .	6.67 ± 0.29	6.62 ± 0.18	6.34 ± 0.19
2. Albumin . . .	3.76 ± 0.24	3.63 ± 0.17	3.32 ± 0.20
3. α_1 -globulins . . .	0.24 ± 0.042	0.25 ± 0.046	0.29 ± 0.042
4. α_2 „ . . .	0.64 ± 0.070	0.64 ± 0.059	0.69 ± 0.056
5. β „ . . .	0.90 ± 0.076	0.87 ± 0.075	0.84 ± 0.066
6. γ „ . . .	1.12 ± 0.075	1.20 ± 0.093	1.20 ± 0.129

The following differences are significant: 1 (b) and 1 (c); 2 (b) and 2 (c); 2 (a) and 2 (c), $P < 0.05$.

the α - and γ -globulins to be raised and the β -globulins to be lowered with more widespread psoriasis. The latter feature is of interest in view of its similarity to the behaviour of serum cholesterol which is also lowered in more widespread psoriasis. This might be expected in view of the relationship of cholesterol to β -lipoproteins.

TABLE V.—*Relationship of Serum Proteins to Progress of Disease (figures g. %).*

	Progress of disease.		
	Improving (a).	Static (b).	Worsening (c).
1. Total proteins . . .	6.39 ± 0.33	6.59 ± 0.17	6.50 ± 0.18
2. Albumin . . .	3.60 ± 0.30	3.68 ± 0.13	3.36 ± 0.20
3. α_1 -globulins . . .	0.21 ± 0.04	0.24 ± 0.03	0.30 ± 0.04
4. α_2 " . . .	0.54 ± 0.09	0.67 ± 0.04	0.67 ± 0.05
5. β - " . . .	0.80 ± 0.08	0.88 ± 0.05	0.88 ± 0.06
6. γ - " . . .	1.17 ± 0.15	1.13 ± 0.06	1.24 ± 0.10

Differences between 4 (a) and 4 (b) and 4 (a) and 4 (c) are significant, $P < 0.02$, $P < 0.05$ respectively.

Table V shows how the proteins vary with the progress of the disease. It shows that albumin is lowered and the α -globulins are raised in psoriasis which is getting worse. It seems likely that the same is true of β - and γ -globulins, but this is uncertain.

Uric acid.—The mean value of the serum uric acid in this series is 4.34 mg. % with a standard deviation about the mean of 0.96. The uric acid levels are not related to the extent or the progress of the disease, as is shown in Table VI.

TABLE VI.—*Serum Uric Acid in Psoriasis in Relation to Extent and Progress of Disease.*

	Extent of disease.		
	Slight.	Moderate.	Widespread.
Serum uric acid . . .	4.3 ± 0.41	4.3 ± 0.41	4.4 ± 0.37
	Progress.		
	Improving.	Static.	Worsening.
Serum uric acid . . .	4.2 ± 0.67	4.2 ± 0.31	4.5 ± 0.40

DISCUSSION.

The serum cholesterol of psoriatics has been reported to be raised (Grütz and Bürger, 1933; Lévy-Francé and Breant, 1948; Versari, 1936; Radl, Kraus and Tousek, 1957), normal (Madden, 1939; Castro-Mendoza and Gomez Orbaneja, 1946; Dodds, MacCormac and Robertson, 1942; Lea, Cornish and Block, 1958) and lowered (Rosen, Rosenfeld and Krasnow, 1937).

The serum uric acid has been reported to be raised (Lobitz and Brunsting, quoted by Ormsby and Montgomery, 1954; Steinberg, Becker, Fitzpatrick and Kierland, 1951) and unaffected (Lea, Curtis and Bernstein, 1958).

As far as serum proteins are concerned (restricting ourselves to fairly recent investigations using electrophoretic separation) Lever, Schulz and Hurley (1951) found moderately increased α_1 and α_2 -globulins in uncomplicated psoriasis. Bolgert, Blamoutier and Moret (1954) found an increase of β -globulins in 50% of cases. Lea, Cornish and Block (1958) found insignificant changes while Kalz, Quastel, Telner, Schafer and MacIntyre (1958) found significant increases in β -globulins. Radl, Kraus and Toussek (1957) state that proteins are normal but Schneider (1955) found a decrease in albumin and an increase in globulins. Ricciardi (1952) also found low albumin with low α - and β -globulins and raised γ -globulins.

Our own findings with regard to serum proteins are quite definite, namely lowered total protein and lowered serum albumin with a rise in the α_2 and β -globulins. These findings can be stated with confidence since we have simultaneously studied a group of similar age and sex distribution.

As regards the serum uric acid and the serum cholesterol, for which we have used standard techniques, we are dependent on others for the normal range. Up to quite a short time ago, the accepted normal value for serum uric acid was up to 5 mg.%. Recent work (Stecher, Hersch and Solomon, 1949) has inclined some to the belief that the normal range extends as high as 6.5 mg.%. It is not completely clear if this belief is justified since although these authors' series of over 1000 subjects comprised patients from medical wards in whom there was no suspicion of gout or nitrogen retention, they were not normal healthy individuals.

If we accept the former figures, 20% of psoriatics have a raised uric acid while if the latter figure is correct the percentage of psoriatics with abnormal uric acid levels drops to 3%, as expected for a "normal" distribution.

Serum cholesterol varies with age and environment and possibly with race. Three sets of figures are available for British people in the past decade as shown in Table VII.

TABLE VII.—*Normal Serum Cholesterol in Britons.*

Authors	Subjects (men).	Age (years).	Mean serum cholesterol (mg. %)
Tanner (1951)	46	18-36	190 $\pm$ 8.6
Keys and Keys (1954)	48	40-55	250 $\pm$ 11.6
Oliver and Boyd (1955)	50	Mean 41	193

Combining these we find a mean serum cholesterol of 211 mg.%. This may be compared with the mean value in our series of 234 mg.% for mild psoriatics and 198 mg.% for those with extensive disease. It thus appears that two

processes are at work in psoriasis, one—perhaps the more fundamental—associated with a raised serum cholesterol and another, present in extensive disease, tending to lower the serum cholesterol. It is tempting to believe that the second factor is related to the observed richness in sudanophilic material of psoriatic lesions (Grütz, 1938; Steigleder, 1952 and Dogliotti, 1953).

As a result of our findings, we tend to the belief that psoriasis is associated with some abnormality of lipide metabolism, but whether the latter has any aetiological relationship to the former is more doubtful. Our observations on the variation of the serum cholesterol and some of the protein fractions with the extent and progress of the disease help to explain certain of the contradictions in the work published on this subject. Other reasons for such anomalies are the inadequate numbers of patients investigated in some series, acceptance of different "normal" standards and frequently, very different conclusions are drawn from very similar observations.

SUMMARY.

1. The serum cholesterol, uric acid and proteins of 86 psoriatics have been studied.
2. The serum cholesterol is raised in 20% of cases. This rise is most evident in cases with minimal lesions (32%) and least apparent with extensive skin involvement (10%).
3. Serum protein levels show decreased total protein and albumin, with raised α_2 - and β -globulins. The more widespread the disease the greater the extent of these abnormalities except for the β -globulins which tend to decrease in widespread disease.
4. The serum uric acid is raised above 5 mg.% in 21% of cases, but above 6.5 mg.% in only 4% of cases. In view of recent work on normal values for blood uric acid, it is considered unlikely that hyperuricaemia is a significant phenomenon in psoriasis.
5. The many contradictions in the literature on the subject of this paper are discussed and an explanation of the anomalies encountered is attempted.

REFERENCES.

- BOLGERT, M., BLAMOUTIER, J. and MORET (1954) *Ann. Derm. Syph., Paris*, **81**, 616.
 BROWN, H. (1945) *J. biol. Chem.*, **158**, 601.
 CASTRO-MENDOZA, H. J. and GOMEZ ORBANEJA, J. (1946) *Rev. clin. españ.*, **21**, 296.
 DODDS, E. C., MACCORMAC, H. and ROBERTSON, J. D. (1942) *Brit. J. Derm.*, **54**, 212.
 DOGLIOTTI, M. (1953) *Hautarzt*, **4**, 17.
 GRÜTZ, O. (1938) *Arch. Derm. Syph., Berlin*, **177**, 246.
 ——— and BÜRGER, M. (1933) *Klin. Wschr.*, **12**, 373.
 KALZ, F., QUASTEL, J. H., TELNER, P., SCHAFER, A. and MACINTYRE, W. (1958) *J. invest. Derm.*, **31**, 161.
 KEYS, A. and KEYS, M. H. (1954) *Brit. J. Nutr.*, **8**, 138.
 LEA, W. A., CORNISH, H. H. and BLOCK, W. D. (1958) *J. invest. Derm.*, **30**, 181.
 ——— CURTIS, A. C. and BERNSTEIN, I. A. (1958) *Ibid.*, **31**, 269.

- LEVER, W. F., SCHULTZ, E. L. and HURLEY, N. A. (1951) *Arch. Derm. Syph., Chicago*, **63**, 702.
- LÉVY-FRANCKEL, A. and BREANT, P. (1948) *Ann. Derm. Syph., Paris*, **8**, 109.
- MADDEN, J. F. (1939) *Minn. Med.*, **22**, 381.
- OLIVER, M. F. and BOYD, G. S. (1955) *Brit. Heart J.*, **17**, 299.
- ORMSBY, O. S. and MONTGOMERY, H. (1954) *Diseases of the Skin*, Eighth Edn. London : Henry Kimpton.
- RADL, J., KRAUS, Z. and TOUSSEK, M. (1957) *Derm. Wschr.*, **64**, 275.
- RICCIARDI, L. (1952) *G. ital. Derm. Sif.*, **93**, 154.
- ROSEN, I., ROSENFELD, H. and KRASNOW, F. (1937) *Arch. Derm. Syph., Chicago*, **35**, 1093.
- SACKETT, G. E. (1925) *J. biol. Chem.*, **64**, 203.
- SCHNEIDER, R. (1955) *Arch. klin. exper. Derm.*, **202**, 110.
- STECHER, R. M., HERSH, A. H. and SOLOMON, W. M. (1949) *Ann. intern. Med.*, **31**, 595.
- STEIGLEDER, G. K. (1952) *Arch. Derm. Syph., Berlin*, **194**, 296.
- STEINBERG, A. G., BECKER, W., FITZPATRICK, T. B. and KIERLAND, R. R. (1951) *Amer. J. human Genetics*, **3**, 267.
- TANNER, J. M. (1951) *J. Physiol.*, **115**, 371.
- TICKNER, A., McCABE M. G. P., and MIER, P. D. (1959) *Brit. J. Derm.*, **71**, 351.
- VERSARI, A. (1936) *Arch. ital. Derm.*, **12**, 639.

SERUM PROTEINS AND LIVER FUNCTION IN EXFOLIATIVE DERMATITIS.

A. TICKNER AND A. BASIT.

Division of Chemical Pathology, St. John's Hospital for Diseases of the Skin,
Homerton Grove, London, E.9.

During the course of investigations in this laboratory into the serum proteins, fractionated by paper electrophoresis, of patients with skin disease, it was noticed that marked changes occurred in cases of exfoliative dermatitis. Reference to the literature showed that a fall in total proteins and in serum albumin had often been reported (Mulvehill, 1944; Posborg Petersen and Schønheyder, 1947; Beek, 1949; Pegum, 1951; Bauer, 1953; and Wilson, 1954). The possibility has frequently been considered that the hypoproteinemia may be due to malfunction of the liver.

Fatty infiltration and cloudy swelling of the liver have been seen *post mortem* in some cases of exfoliative dermatitis (Poole and Wegher, 1934; Butterworth, 1936; Wilson, 1954) and pathological changes have also been seen in liver biopsies in this condition (Pegum, 1951). The results of chemical liver function tests have been equivocal. The older work may perhaps be safely ignored owing to the lack of sensitivity and of specificity of the tests used. Of later workers, Bauer (1953) has specifically studied liver function in exfoliative dermatitis. He reported on serum proteins, "empirical" tests, alkaline phosphatases, urinary urobilin and hippuric acid excretion in ten cases. He found a significant decrease of serum albumin and of hippuric acid excretion and in individual patients this decrease was correlated with the severity of the disease.

We decided to investigate larger numbers of patients, fractionating the serum proteins by paper electrophoresis and employing estimations of serum cholinesterase, thymol turbidity, bromsulphthalein excretion and hippuric acid excretion as tests of liver function. Of these the serum cholinesterase appeared peculiarly relevant since there is evidence to show that the synthesis of this protein, which takes place exclusively in the liver, is impaired before the synthesis of serum albumin is affected (Hutchinson, McCance and Widdowson, 1951; McCardle, 1940).

INVESTIGATION.

A total of 36 patients was investigated although for various reasons not all tests were carried out on each patient. However, there were finally available for analysis the results of 24 estimations of serum proteins, 32 of serum choline-

sterase, 36 of thymol turbidity, 31 of bromsulphthalein excretion and 10 of hippuric acid excretion.

In addition the serum proteins of 27 normal individuals were estimated as were the serum cholinesterase levels of 10 of these normals. The latter are not reported here, since they fall into the range (50–100 μ l CO₂/ml./min.) expected as the result of previous experience of one of us (A. T.) stretching over some years.

Methods.

Total serum proteins were measured by the biuret method of Wolfson, Cohn, Calvary and Ichiba (1948) checked weekly by determinations on the standard freeze-dried serum of the Association of Clinical Pathologists supplied by Messrs. Glaxo. Protein fractionation was carried out on Whatman No. 1 paper by a slight modification of the method of Jencks, Jetton and Durum (1955) using an EEL paper electrophoresis bath and scanner. Serum cholinesterase was measured manometrically by the method of Ammon (1934) using acetylcholine as substrate. Thymol turbidity was estimated by the method of MacLagan (1944). The bromsulphthalein excretion test was carried out by the method of Mateer *et al.* (1942). Quick's hippuric acid excretion test was used according to Varley (1954). Results are shown in Tables I–IV.

DISCUSSION.

Serum protein levels are significantly changed in exfoliative dermatitis, the total protein and serum albumin being lowered while all fractions of the globulins are raised (Tables I (a) and I (b)). This is the stereotyped pattern seen so frequently in systemic disease. In individual cases, the most striking phenomenon is the drop in serum albumin seen in 67% of this series (Table IV).

Only four patients (11%) in this series showed liver dysfunction detected by the tests used. It seems unlikely that so marked a change in serum albumin, if it were due to liver dysfunction, would so rarely be accompanied by other manifestations of liver derangement.

The serum protein pattern might be thought to be that so often seen in infection but the rise in the α - and γ -globulin fractions is not marked, so that infection would not appear to be of great importance in this connection.

The total body serum albumin is about 250 g. and normally about 20 g./day are made and destroyed (Sterling, 1951). Assuming that the distribution of albumin is the same in patients with exfoliative dermatitis as in normal people, that the total body fluids are not increased in exfoliative dermatitis, that the synthesis of albumin by the liver is constant, and that the disappearance of serum albumin is a direct function of its level in the blood, it can be calculated that the increased loss of serum albumin would need to be 7 g./day to reach the mean level in exfoliative dermatitis. This is a modest increase relative to the 20 g. of protein a day lost by the patient by desquamation (Peters 1945 ;

TABLE I (a) : *Normal Serum Protein Levels (g./100 ml.) 27 individuals.*

Fraction.	Mean value.	Standard deviation.	Observed range.
Total	6.80	0.355	6.0-7.6
Albumin	4.14	0.383	3.4-4.8
Globulins	2.66	0.383	1.8-3.5
α_1 -globulin	0.225	0.0794	0.1-0.4
α_2 "	0.550	0.132	0.3-0.8
β - "	0.727	0.110	0.5-0.9
γ - "	1.104	0.247	0.6-1.5

TABLE I (b) : *Serum Protein Levels in Exfoliative Dermatitis (g/100 ml.) (24 Cases).*

Fraction.	Mean value.	Standard deviation.	Observed range.
Total	6.163	0.718	4.7-7.6
Albumin	3.09	0.631	2.1-4.2
Globulins	3.07	0.631	2.4-4.3
α_1 -globulin	0.315	0.089	0.1-0.4
α_2 "	0.671	0.165	0.3-1.0
β - "	0.771	0.221	0.3-1.5
γ - "	1.28	0.475	0.6-2.6

TABLE II : *Probability that the Observed Differences between the Means in Tables I (a) and I (b) are Due to Chance.*

Fraction.	P.
Total proteins	<0.001
Albumin	<0.001
Globulin	<0.001
α_1 -globulin	<0.001
α_2 "	<0.001
β - "	<0.001
γ - "	<0.001

TABLE III : *Results of Liver Function Tests.*

Test.	Number of cases.	Number abnormal.	Criterion of abnormality.
Serum cholinesterase	32	3*	<50 μ l. CO ₂ /ml./min.
Thymol turbidity	36	2*	>4 units.
Bromsulphthalein excretion	31	0	>5% retained after 45 minutes.
Hippuric acid excretion	10	0	>3.5 g. excreted in 4 hours.

* One patient had both a lowered serum cholinesterase and a raised thymol turbidity.

TABLE IV.—*Percentage of Cases of Exfoliative Dermatitis showing Specified Abnormality.*

Abnormality	% cases.
Lowered total protein	37
" serum albumin	67
Raised " globulin	25
" α_1 - "	0
" α_2 - "	17
" β - "	17
" γ - "	17
Lowered serum cholinesterase	9
Raised thymol turbidity	6
Lowered bromsulphthalein excretion	0
" hippuric acid excretion	0

Posborg Petersen and Schönheyder, 1947 and Pegum, 1951). Indeed if we make the further reasonable guess that the serum albumin forms a source from which the skin derives some of its amino acids, it appears probable that so far from diminishing in exfoliative dermatitis, the synthesis of serum albumin by the liver may well be increased.

SUMMARY.

Thirty-six cases of exfoliative dermatitis have been studied with regard to serum protein levels or liver function tests or both.

Considered as a group compared with a group of normal subjects, the cases of exfoliative dermatitis show a significant decrease in total proteins and serum albumin and a significant rise in all of the globulin fractions. The change most frequently met with in the individual case is a fall in serum albumin.

The liver function has been investigated by measuring serum cholinesterase, thymol turbidity, bromsulphthalein excretion and hippuric acid synthesis. In 88% of cases no disturbance of liver function could be demonstrated.

It is concluded that the most probable explanation of the lowered serum albumin is that it is due to loss through or use by the skin.

REFERENCES.

- AMMON, R. (1934) *Pflüg. Arch. ges. Physiol.*, **233**, 486.
 BAUER, F. (1953) *Aust. J. Derm.*, **2**, 69.
 BECK, C. H. (1949) *Dermatologica, Basel*, **99**, 372.
 BUTTERWORTH, T. (1936) *Arch. Derm. Syph., Chicago*, **34**, 676.
 HUTCHINSON, A. O., McCANCE, R. A. and WIDDOWSON, E. M. (1951) Medical Research Council, Special Report Series, No. 275, p. 216.
 JENCKS, W. P., JETTON, M. R. and DURRUM, E. L. (1955) *Biochem. J.*, **60**, 205.
 MCARDLE, B. (1940) *Quart. J. Med., N.S.* **9**, 107.
 MCLAGAN, N. F. (1944) *Brit. J. exp. Path.*, **25**, 234.
 MATEER, J. G., BALTZ, J. I., MARION, D. F., HOLLAND, R. A. and YAGLE, E. M. (1942) *Amer. J. digest. Dis.*, **9**, 13.
 MULVEHILL, W. (1944) *Arch. Derm. Syph., Chicago*, **49**, 327.
 PEGUM, J. S. (1951) *Guy's Hospital Reports*, **100**, 304.
 PETERS, B. A. (1945) *Lancet*, **i**, 265.
 POOLE, A. K. and WEGHER, R. T. (1934) *J. Amer. med. Ass.*, **102**, 745.
 POSBORG PETERSEN, V. and SCHÖNHEYDER, F. (1947) *Acta derm.-venereol., Stockh.*, **27**, 497.
 STERLING, K. (1951) *J. clin. Invest.*, **30**, 1228.
 VARLEY, H. (1954) *Practical Clinical Biochemistry*, 2nd edn. London: Heinemann.
 WILSON, H. T. H. (1954) *Arch. Derm. Syph., Chicago*, **69**, 577.
 WOLFSON, W. Q., COHN, C., CALVARY, E. and ICHIBA, F. (1948) *Amer. J. clin. Path.*, **18**, 723.

THE GLUCOSE TOLERANCE CURVE IN HIDRADENITIS SUPPURATIVA.

R. M. B. MACKENNA, M.A., M.D., F.R.C.P.

AND

H. LEHMANN, M.D., Sc.D., M.R.C.P., F.R.I.C.

St. Bartholomew's Hospital, London.

By the term hidradenitis suppurativa we refer to chronic abscess formation usually occurring in the axillae, but occasionally involving other sites, believed to be caused by bacterial infection of the apocrine sweat glands.

Our observations extend over a period of nearly three years, and were it not for the great dearth of clinical material we should certainly not venture to publish this note : but even with the generous co-operation of other dermatologists outside our hospital we have not, in this period, seen as many cases as we would have liked to record.

Our interest was aroused when we noted that the blood sugar curve was surprisingly flat in two women suffering from suppurative hidradenitis. They were under investigation merely because of the chronicity of their lesions, but otherwise appeared to be healthy. We could not recognize any immediate connection between the abnormality of sugar utilization suggested by this curve and the apocrine infection ; but this type of flat curve has been noted in the tropics in patients suffering from nutritional deficiencies and certain cutaneous maladies, who improved greatly on an adequate diet, particularly one reinforced by the addition of riboflavine. This vitamin was, therefore, given to our patients, in doses of 3 mg. thrice daily. In six of our small series of seven cases the treatment appeared to be satisfactory, the lesions slowly disappearing whilst the diet was supplemented in this way ; the seventh has not been treated with riboflavine. After several months we could usually, but not invariably, stop the riboflavine without relapse of the malady.

All seven patients were women, the youngest was aged 19 and the oldest 52. Fig. 1 shows their response to 50 g. glucose by mouth. It will be seen that five curves are flat, one is the very opposite being of the "lag" or "steeple" curve type and one is diabetic, but none is normal. Although the skin condition responded to riboflavine in the six non-diabetic cases, the type of blood sugar tolerance curve did not alter ; but in one instance it seemed that on repeating the test after one and two years, the sugar curve had become slightly less flat. The diabetic case has not been under observation or treatment

for a sufficiently long period for us to make any comment concerning her progress.

One of the six patients consented to enter the hospital for further investigation of the abnormal glucose tolerance. It was possible to show that the flat curve was not due to hyperinsulinism, or to increased sensitivity to insulin; two insulin tolerance tests gave normal results. The absorption defect did not seem to be restricted to glucose, but also applied to the fat-soluble vitamin A. In the vitamin A absorption test, the fasting blood specimen contained 140 International Units (I.U.) per 100 ml. serum. Five hours after oral administration of 350,000 I.U. of vitamin A, the level had only risen to 182 I.U. per 100 ml. serum.

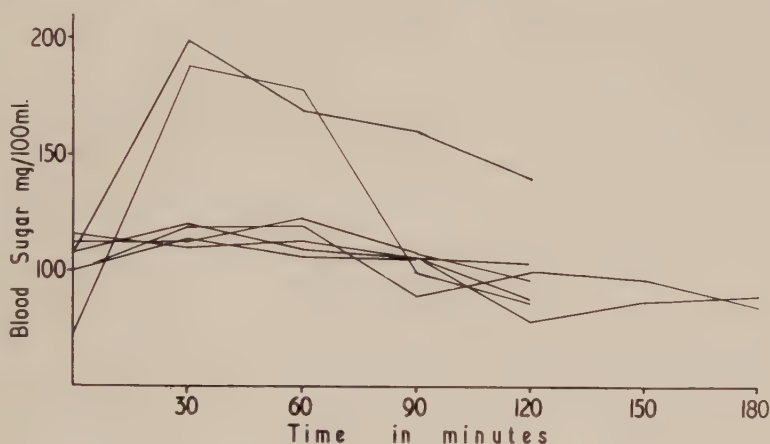


FIG. 1.

It was remarkable that the two patients who did not have a flat blood sugar tolerance curve showed the very opposite. One had a "lag" curve with a rise from 73 mg. per 100 ml. when fasting, to 188 mg. per 100 ml. within half an hour after administration of 50 g. glucose. The other had a mild diabetic curve with a rise of 91 mg. per cent. within the first half-hour and failure to return to the fasting level (107 mg. per cent.) after two hours; the blood sugar level at the end of these two hours was 140 mg. per cent. If, in the other five women, utilization of glucose by the intestinal mucosa was deficient, perhaps in these the intestinal barrier was overcome, but there was a lessened ability of muscle and liver to utilize the absorbed hexose.

Dr. Brian Russell gave us the opportunity to examine a woman who had suffered from hidradenitis suppurativa in the past. The condition had been so severe that plastic surgery had been necessary in the axillae and vulva. When we saw her, she had been well for some two years; her blood sugar tolerance test was normal.

SUMMARY.

In a small series of cases of hidradenitis suppurativa an inability to utilize glucose normally was observed. The majority showed a flat blood sugar curve. Because of this, we decided to try the effect of riboflavine in small doses given orally ; clinically the result was satisfactory. In two cases, one showed a lag curve and responded to riboflavine ; the other was diabetic and has only recently come under observation.

THE IRON CONTENT OF FINGER NAILS.

ALLAN JACOBS, M.D.

Department of Pathology, Paddington General Hospital, London, W.9

AND

D. J. JENKINS, F.I.M.L.T.

Late Department of Chemical Pathology, The Hospital for Sick Children,
Great Ormond Street, London, W.C.1.

It has long been known that an appreciable amount of iron is found in the epidermis (Rothmann and Schaaf, 1929) but no simple method has been described for its quantitative estimation. The nails form by keratinization of epidermal cells and therefore derive their iron content entirely from the epidermis. The amount of iron in nails probably reflects the epidermal concentration.

INVESTIGATION.

Iron in finger nails was estimated in a series of 100 normal subjects, comprising 56 males and 44 females of up to 84 years of age, including two premature infants. Estimations were also made in 35 patients suffering from severe iron-deficiency anaemia. Specimens were obtained by clipping the finger nails in the usual way. After the mechanical removal of dirt and varnish, the clippings were washed thoroughly in three changes of water, to the first of which a small volume of Teepol was added. This was followed by three changes of ether and another three changes of distilled water. The nails were dried at 60° C. and weighed; 20-30 mg. of nails were digested with 2 ml. of a mixture of perchloric acid 30 ml. and concentrated nitric acid 50 ml. on a sand bath at 35° C. until a dry residue was obtained. This was dissolved in 2 ml. of distilled water and the concentration of iron was measured by the method of Ramsay (1957) using *aa'* dipyrldyl as the colour reagent; 2 ml. of digestion mixture treated in the same way was used as a blank. Results were expressed as $\mu\text{g. Fe/g. dry nail}$.

RESULTS.

In the group of normal subjects, no difference in the iron content of nail was found between the two sexes. There was a wide scatter of results in all age groups. The results, grouped by age, are plotted in Fig. 1 and the mean value in each age group is shown in Table I. By far the highest levels were found during infancy, especially in the neonatal period where amounts of nail iron over 1000 $\mu\text{g./g.}$ were not uncommon. The level fell to a minimum in adolescence and thereafter rose slightly to remain fairly stable throughout adult life.

The iron concentrations in the anaemic group are shown in Fig. 2 where they are compared with the curve of mean values in normal subjects. In

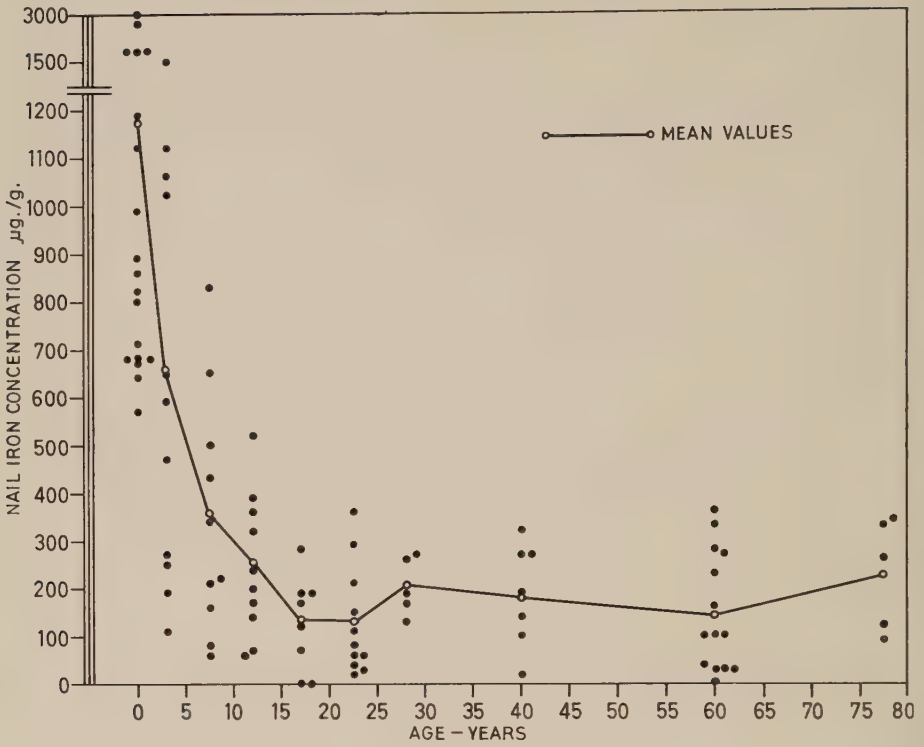


FIG. 1,

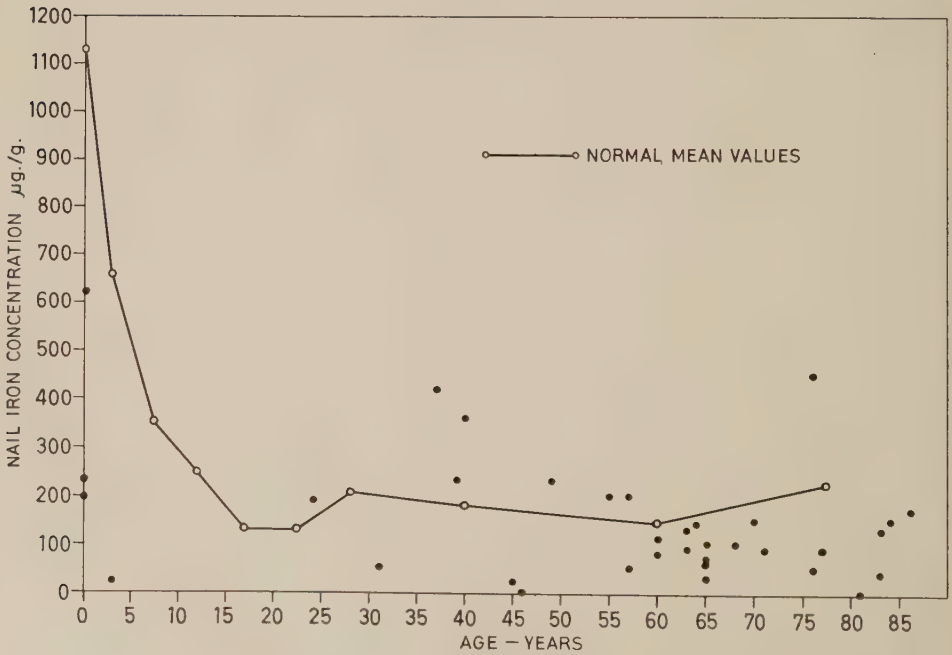


FIG. 2.

childhood and in later life most of the values obtained fell below the normal mean but in the age group 20-50 years there appeared to be a normal distribution. There is no relationship between the degree of anaemia shown in Table II and the iron content of the nails.

TABLE I.—*Mean Iron Content of Normal Nails at Different Ages.*

	Age (years).									
	Less than 1	1-5	6-9	10-14	15-19	20-25	26-30	31-50	51-70	71+
Number of cases	19	11	10	10	8	11	5	7	14	5
Mean iron concentration ($\mu\text{g./g.}$)	1184	660	351	249	129	129	206	186	147	227

TABLE II.—*Haemoglobin Levels in the Anaemic Patients.*

	Haemoglobin (g.%).										Total.
	3-3.9	4-4.9	5-5.9	6-6.9	7-7.9	8-8.9	9-9.9	10-10.9	11-11.9	12-12.9	
Number of cases	1	5	2	6	8	9	1	2	0	1	35

DISCUSSION.

Probably the greater part of the iron in the epidermis is a constituent of intracellular enzymes and as such plays a vital part in epithelial metabolism. There is no evidence that the iron present in the epidermis and nails forms part of the body stores of this element. No iron stainable by the Prussian Blue reaction is found here normally and only rarely even in conditions such as haemochromatosis, where a gross excess is present in the body.

The process of cornification which takes place when epidermal cells are converted into nail includes dehydration and physical compression of the cellular elements. The inorganic constituents which are transferred from skin to nail probably undergo considerable concentration because of this. The concentration of iron in nail is likely to be much greater than in the epidermis but unless nail formation varies, it should bear a constant relationship to epidermal concentration.

The highest concentration of iron in normal finger nails occurs in the neonatal period and infancy but although the concentration tends to fall throughout childhood, adult levels are not always found until over the age of ten years. This initial high concentration might be associated with the increased metabolic activity that is known to occur in the new-born skin (Barron *et al.*, 1948) and which may be maintained in later childhood (Schultze, 1943). This increase, however, is not of the magnitude suggested by the very high concentrations of iron found in some subjects. It is possible that nail formation is different in children and adults so that the relationship between epidermal and nail iron varies with age.

The reduction of the iron content of the epidermis in iron-deficiency anaemia has already been suggested by the results of Hussain and Patwardhan (1959). They found that the iron content of cell-rich sweat in anaemic patients was lower than that of normal subjects, but that following iron therapy it rose to within the normal range. There is evidence in the results of the present investigation that at some ages there tends to be a reduced iron content in the nails of anaemic patients. The epidermal iron deficiency could be consequent upon the generalized deficiency of iron containing enzymes which has been postulated in this condition. Beutler (1957) has demonstrated a reduction of cytochrome C in the liver and kidney of rats rendered iron deficient and suggests that some of the symptoms of iron deficiency depend on the enzyme lack rather than the anaemia itself.

It is of interest to note that the age group showing the lowest concentration of iron in the nails (15-25 years) is that which sometimes exhibits primary iron-deficiency anaemia (Leonard, 1954; Brumfitt, 1959). This is also the period of rapid adolescent growth.

SUMMARY.

The iron content of finger nails has been measured in 100 normal subjects and an age variation demonstrated. The significance of this is uncertain. In 35 iron-deficient subjects, the content tended to be slightly reduced. This may be secondary to an intracellular iron deficiency in the epidermis.

We should like to thank Dr. R. R. Wilson for his interest and valuable suggestions.

REFERENCES.

- BARRON, E. S. G., MEYER, J. and MILLER, Z. B. (1948) *J. invest. Derm.*, **11**, 97.
BEUTLER, E. (1957) *Amer. J. med. Sci.*, **234**, 517.
BRUMFITT, W. (1959) *Brit. med. J.*, **ii**, 473.
HUSSAIN, R. and PATWARDHAN, V. N. (1959) *Lancet*, **i**, 1073.
LEONARD, B. J. (1954) *Ibid.*, **i**, 899.
RAMSAY, W. N. M. (1957) *Clin. Chim. Acta.*, **2**, 214.
ROTHMANN, S. and SCHAAF, F. (1929) "Chemie der Haut" in Jadassohn's *Handbuch der Haut und Geschlechtskrankheiten*, Vol. I/ii. Berlin: Springer.
SCHULTZE, W. (1943) *Arch. Derm. Syph., Berlin*, **185**, 93.
-

BIOCHEMICAL EXPERIMENTS ON THE BINDING OF CHROME TO SKIN.

F. E. ANDERSON, M.D.

Skin Department, Royal Victoria Hospital and
the Queen's University of Belfast.

It has been shown that a large percentage of sufferers from cement dermatitis are hypersensitive to potassium dichromate (Anderson, 1960). To some extent, therefore, cement dermatitis must be regarded as an allergic eczematous dermatitis.

For many years there has been speculation about the mode of production of allergic eczema. Many workers have carried out experiments to try to establish the presence of antibodies, the site of antibody formation and similar factors usually met with in other allergic diseases. It has frequently been noticed that many of the substances causing allergic eczema are simple chemicals and many of them, as discussed by Haxthausen (1954), have a marked affinity for protein. Chromium and mercury are specially mentioned as such substances. Many authors have given it as their opinion that a chemical substance producing cutaneous sensitization does so by first uniting with some protein molecule in the skin to form a protein complex which acts as the antigen. As long ago as 1935, Landsteiner and Jacobs thought that this was probable in the case of *p*-phenylene-diamine but stated that the assumption was not so obvious for other substances. In 1940, Haxthausen published the results of a series of experiments from which he drew the conclusion that dinitrochlorbenzene, in order to have an antigenic effect, had to be linked to a protein. He showed in the same series of experiments that the protein need not necessarily be foreign to the species, that is, that it was usually the patient's own skin protein which united with the chemical substance.

Sulzberger and Witten (1953) discussed the comparative immunology and morphology of the allergic eczematous process in man. They thought that it was highly probable that the sensitizing properties of the simple chemical substances of low molecular weight must in many, and perhaps all, instances depend on their ability to conjugate with protein or with some other large molecule in the body. It was also stated that the specificity of the complex allergens in anaphylaxis and other classic forms of immunologic reaction is to a great degree independent of the nature of the protein or of the other large molecule but is dependent on the properties of the smaller simple chemical constituent.

However, it has not been definitely proven that linkage to protein is the first stage in the process of eczematous sensitization. In 1921, Whitfield described two cases in which eczema was observed following bruises where the surface was not broken. He produced the hypothesis that these persons had become sensitized to their own damaged tissue. In 1952, Epstein made the point that when the skin is painted with a sensitizing substance, it is usual to assume that the linkage of this substance with protein results in the sensitizing effect. In other words, particular significance has always been attached to the simple chemical substance of which the protein component has been looked upon as the necessary carrier. Epstein suggested that the protein component was probably also altered in such a way as to have an antigenic effect by itself and he called the antigenic protein compound the "protigen". This protigen might then induce the production of one or more antibodies which might possibly react with normal skin protein. This explanation could help in understanding the frequently protracted course of eczemas produced by substances with a marked affinity for protein, e.g. chrome. Epstein's theory is that having been damaged by a simple chemical substance, certain radicals in the protigen convey the specificity while the remainder of the protein molecule acts as a carrier.

The more widely believed theory, however, is that the linkage of the simple chemical substance with the protein molecule to form an antigenic conjugate is the primary step in the series of events leading to eczematous sensitization. In view of the aforementioned theories, it is probable that the first step in chrome sensitivity is the linkage between the chromium and the skin protein. It was thought that it would be of great interest to investigate the part played by the constituent groups of the collagen molecule in the binding of chromium and to this end a study was undertaken of the methods available for estimating chromium bound to skin.

Wells (1956) carried out a series of experiments designed to investigate the effects of nickel on skin. Histochemical methods using dimethylglyoxime or dithio-oxamide as the colour reagent for nickel were employed to demonstrate the distribution of nickel retained in the skin after soaking in 1% nickel sulphate and washing. It was seen that the principal uptake of nickel took place in the deeper parts of the horny layer and in the inner root sheath of hairs. Having developed this technique, Wells continued by applying certain chemicals to the skin in order to see whether any particular chemical group of the horny layer combined with the nickel. The results of these experiments suggested that the carboxyl groups of the horny layer might play a part in nickel binding.

It was considered that in the case of the linkage between chromium and the constituent parts of the collagen molecule, somewhat similar experiments could be carried out. In place of the histochemical techniques of Wells, an

estimation of the amount of chromium in a given weight of skin was to be the index of the effect of the different skin treatments. The next important step was to develop an accurate method for measuring the amount of chromium taken up by skin after soaking in potassium dichromate. The skin used in the experiments was obtained from surgical and *post-mortem* material. It was considered that the skin, taken as soon as possible after death or operation and kept in a deep freeze, would react in a very similar way to living tissue. Flesch (1955) discussed this and performed certain tests of percutaneous penetration on dead skin showing that it was satisfactory material for experiment.

INVESTIGATION.

Method Used to Measure Uptake of Chromium by Skin.

Several methods, including electrometric titration, and ashing and fusing, were tried before a fairly accurate estimation of chromium bound to skin could be carried out.

The final method used in the ensuing experiments was as follows. A strip of skin was first soaked in potassium dichromate, in most cases of N/10 strength, for a period of two hours. The skin was then suspended in a syphon apparatus which filled and emptied with chromium-free tap water approximately twelve times per hour. This washing was continued for 12 hours in order to make sure that only the chromium combined with the skin protein remained to be measured. The skin was then divided into small pieces and dried in an oven at 100° C. for 12 hours. Following this, the small pieces of skin were weighed individually, and it was found that a satisfactory weight was between 0.01 and 0.04 g. The skin samples were then placed separately in Kjeldahl flasks and 0.5 ml. of concentrated sulphuric acid and 5 ml. of concentrated nitric acid added. This mixture was slowly heated over a low flame until all the nitric acid had been boiled off and the white fumes of sulphur trioxide became apparent. Five ml. of distilled water were added and then two drops of potassium permanganate. The flasks were then heated in a water bath for half an hour to ensure that the permanganate oxidized all the chromium to the hexavalent state. One drop of sodium azide served to remove excess permanganate. The solutions were made up to 100 ml. with distilled water containing 0.5 ml. of diphenylcarbazide. The colours were measured on a Hilger Spekker Absorptiometer at 520 m μ . and using the 1 cm. cell. From the data thus acquired and a Standard Chromium Graph the amount of chromium per gram of skin was calculated. Pieces of skin which had not been soaked in chromium solutions gave no colour following this procedure.

Having decided upon the experimental details for the determination of chromium in skin, the method was tested. A piece of skin was soaked for two hours in N/10 potassium dichromate and subsequently washed using the running water technique. Twenty small pieces were cut with a scalpel from the original skin and dried as described. The amount of chromium present per gram was then estimated in each piece of skin. The distribution of these twenty observations was then statistically tested for normality. A coefficient of variation of 9% suggested that the results would be sufficiently accurate for the interpretation of the effects of the different treatments on the chromium uptake of skin.

Experiments on Skin.

Having developed a suitable method for determining the amount of chromium bound to skin, it was decided to try the effect of different biochemical treatments on the binding power of the skin. Most of these treatments were aimed at blocking off one or other constituent group of the collagen molecule. In each case it was necessary to have a control. Two pieces of skin from the same source were used for each experiment and one underwent the treatment while the other acted as a control. Each piece of skin was then soaked in 25 ml. of the same chromium solution for two hours following which they were washed together for twelve hours in the manner described. The skin samples were then divided up and dried on separate Petrie dishes in the same oven at approximately 100° C. for twelve hours. After drying, the chromium estimations were carried out as described. In each experiment, a comparison was made between six estimations on the experimental sample and six on the control. In the following description of the experiments the significance of the difference between the means in each comparison was evaluated by using double-sided *t*-tests. The one in twenty level of significance was employed in these tests.

Before carrying out the experiments to block off different constituents of the collagen molecule it was necessary to evaluate the effect of pH on chromium uptake. To do this four samples of skin were soaked in N 100 potassium dichromate made up in Sorensen's buffers at pH 2, pH 5, pH 9 and pH 12. A *t*-test was made between each pH and its adjacent pH and there was a significant trend of results with the greater uptake at the lower pH values. As many of the intended skin treatments involved quite marked changes of pH, it was therefore necessary to attempt to adjust both the treated and the control skin in each case to the same pH. This was done by soaking the skin samples in Sorensen's pH 7 buffer for thirty minutes. The buffer solution was then renewed and the skin allowed to sit overnight. Following this the chromium uptake was estimated as before. It will be noticed that skins from different sources take up markedly different amounts of chromium.

Treatments (see Table I).

(i) Sulphydryl blockage. This was attempted by soaking the skin in 5% iodoacetamide in alcohol for 24 hours (Wells, 1956). The control skin sample was soaked in alcohol for the same period. This treatment did not affect the uptake of chromium by skin.

(ii) Sulphydryl release. Reduction of disulphide groups with alkaline sulphite causes sulphydryl release (Wells, 1956). The skin was soaked in 0.05% sodium sulphite in N/100 sodium hydroxide for 2 hours. The control skin was soaked in N/100 sodium hydroxide for the same period. This treatment did not affect the chromium uptake.

TABLE I.—*Chromium Content of Skin after Various Biochemical Treatments.*

Treatment.	Means.		Probability.
	Test skin ($\mu\text{g./g.}$).	Control skin ($\mu\text{g./g.}$).	
Sulphydryl blockage . . .	2452.17	2548.00	$0.5 > P > 0.4$
Sulphydryl release . . .	680.33	679.83	$P > 0.9$
Deamination . . .	1140.50	1113.33	$0.8 > P > 0.7$
Methylation . . .	1599.83	1164.50	$P < 0.001^*$
Benzoylation . . .	1660.33	1161.17	$P < 0.001^*$
Extraction of lipids . . .	702.00	684.17	$0.4 > P > 0.3$
Reducing substance . . .	1057.33	1065.17	$P > 0.9$

Significant at 5% level. The significance has been tested using double-tailed *t*-tests.

(iii) Deamination. This was carried out with the Van Slyke's nitrous acid reagent (Peters and Van Slyke, 1932). The conclusion was that deamination did not increase the chromium uptake of skin.

(iv) Methylation. The test skin was soaked in dry methanol containing N/10 hydrochloric acid for 4 days at 37° C. (Lillie, 1954). This treatment was found to increase the uptake of chromium from a potassium dichromate solution.

(v) Benzoylation. In this case the skin was soaked for 24 hours in a mixture of 90 ml. dry pyridine and 10 ml. benzoyl chloride (Pearse, 1953). This treatment was seen to increase the uptake of chromium from potassium dichromate.

(vi) Extraction of lipids. Intensive extraction of lipids was attempted by methods described by Pearse (1953). The skin sample was soaked in dry pyridine for 30 minutes at 20° C. and then immersed in another sample of pyridine and left for 24 hours at 60° C. This caused no change in the chromium uptake of skin.

(vii) The presence of a reducing substance. To 25 ml. of N 10 potassium dichromate 0.6 g. of sodium sulphite was added and the test skin soaked in it. This did not affect chromium uptake.

It was shown in clinical studies (Anderson, 1960) that those patients who are sensitive to potassium dichromate are not also sensitive to chromium chloride. It was thought that it would be of interest to see whether a different binding mechanism for cationic chromium could be demonstrated. For this reason further experiments were carried out.

A comparison between the uptake from potassium dichromate and that from chromium chloride showed that the skin takes up more chromium from a solution of trivalent chromium than from one of potassium dichromate containing the same amount of elemental chromium (chromium chloride, 3682.7 $\mu\text{g. g.}$, potassium dichromate, 1724.33 $\mu\text{g. g.}$, $P < 0.001$). The effect of pH on the uptake from chromium chloride was tested by carrying out the experiment at pH 2 and pH 9. No difference in uptake was observed (at pH 2, 243.33 $\mu\text{g. g.}$, at pH 9, 250.5 $\mu\text{g./g.}$, $0.70 > P > 0.60$). The uptake of chromium following deamination, methylation and benzoylation was increased, but was diminished in the presence of a reducing agent (Table II).

TABLE II.—*Chrome Content of Skin after Various Biochemical Treatments Using Chromium Chloride Solutions.*

Treatment.	Means.		Probability.
	Test skin ($\mu\text{g./g.}$).	Control skin ($\mu\text{g./g.}$).	
Deamination . .	2122.33	1357.67 .	$P < 0.001^*$
Methylation . .	2228.17	1772.83 .	$P < 0.001^*$
Benzoylation . .	1397.33	711.83 .	$P < 0.001^*$
Reducing agent . .	702.50	1446.33 .	$P < 0.001^*$

* Significant at 5% level.

DISCUSSION.

These biochemical studies were designed to investigate the scientific basis of some clinical observations which have been made concerning cement dermatitis. These may be briefly summarized as follows.

Cement dermatitis occurs less frequently as a result of contact with dry than with wet cement. It would thus appear that chromium solutions formed

in contact with the skin surface are less allergenic than the more alkaline solutions represented by wet cement.

The presence of hexavalent chromium is probably necessary for the production of dermatitis and it is doubtful whether it occurs as a result of contact with solutions containing trivalent chromium.

Cement dermatitis has been shown to be chronic in nature and this suggests a permanent binding of the chromium to the molecular structure of the skin.

The experiments designed to investigate the effect of the pH of the applied chromium solutions show that much more chromium is taken up at acid than at alkaline pH when the chromium is in the hexavalent state. In trivalent chromium solutions pH makes no such difference. But in no case has it been found that the uptake is greater in alkaline solutions. This is at variance with the observed clinical data where it is quite clear that dermatitis occurs more readily as a result of contact with alkaline cement solutions than with pure chromium solutions at their inherent pH. There is thus the implication that the production of dermatitis is not quantitatively related to the amount of chromium taken up by the skin and must involve other factors. Gustavson (1956) in considering the chromium tanning process for leather has shown that while a change of acidity has little effect on the chromium uptake of collagen treated with solutions of cationic chromium, the amount of non-ionic chromium taken up is considerably increased by pre-treatment of the collagen with increasing amounts of acid. He ascribes this to the effect of the acid treatment in breaking the hydrogen bonds which represent the main cohesive and inter-chain linkages of the collagen molecule with the result that the chains take up a disordered arrangement which presents more reactive groups to the action of the materials to be bound. While this accords well with the above findings showing an increased uptake of chromium from dichromate solutions at acid pH, it serves to underline the complex nature of the production of dermatitis where the effect of pH is reversed.

The experiments carried out to compare the behaviour of cationic trivalent chromium chloride solutions with solutions of potassium dichromate in which the chromium is in the form of a complex hexavalent anion show that the mechanism of trivalent chromium binding is different in some respects from that occurring with the anionic form. This is shown particularly in the effects of prior deamination, change of pH and the presence of a reducing substance. This is again in complete agreement with the findings of Gustavson whose figures show that the uptake of chromium by collagen from purely cationic trivalent solutions is much less than the fixation from non-ionic solutions in which the chromium co-ordinates to take up the hexavalent form.

This difference in binding mechanism is probably the explanation of the fact that patients with cement dermatitis show positive patch tests to potassium dichromate and not to chromium chloride. This is the more striking

in view of the experiment described earlier in which a direct comparison was made between the uptake of skin from chromium chloride solutions as opposed to solutions of potassium dichromate. The finding that the uptake is greater from the trivalent chromium chloride solutions is in complete opposition to the findings of Gustavson for collagen.

All the investigations of the effect of sulphhydryl groups, whether by selective treatment with iodoacetamide or by reduction of disulphide linkages already present, showed that these groups do not influence chromium binding. It is interesting in this connection that Flesch *et al.* (1955) were able to show an excellent correlation between the penetrating ability and sulphhydryl inactivating capacity of potassium dichromate. In other words, increased binding of chromium resulted in a reduction in the number of sulphhydryl groups present.

Inactivation of the carboxyl groups was carried out by selective methylation using methanol in hydrochloric acid solution. It has been shown by Fraenkel-Conrat and Olcott (1945) that this procedure does not affect either amino or amide groups and achieves almost complete esterification as estimated by comparing the number of methoxy groups introduced with the number of carboxyl groups in the collagen molecule. When this procedure is carried out with animal collagen, the resulting esterified product does not take up chromium from solutions containing the element in cationic form (Gustavson, 1952) whereas in the experiments described here there is a highly significant increase in the uptake of cationic chromium by skin after the methylation process. Anionic chromium is also taken up in greater quantities after this procedure. This can possibly be explained by the effect of methylation in rupturing the hydrogen bonds, with consequent transformation of the molecule into a disordered form in which new binding sites become available.

Deamination of the skin involves inactivation of the E-amino group of the lysine radical by treatment with nitrous acid. The procedure is not quite specific in that some portions of the guanidyl groups are removed at the same time. Since the guanidyl group of collagen is the site of marked cross-linking, the process of deamination undoubtedly has the secondary effect of extensive rupture of cross linkages. It is possible to regard the increased chromium uptake from cationic chromium solutions after deamination as proof that deamination, by freeing the carboxyl groups involved in peptide linkages, makes available the latter group for chromium binding. However, the extensive rupture of cross linkages which also occurs must throw doubt on the validity of this explanation.

The experiments involving benzylation which should act on amino or hydroxyl groups show that in all cases the effect of the treatment is to increase the amount of chromium taken up by skin. Again the effect is probably due to the freeing of carboxyl groups for binding by the inactivation of hydroxy and amino groups.

As a corollary to the experimental work on treatment of the skin with specific inactivating agents, it is important to notice that the influence of the other materials present in cement in facilitating the contact of the chromium itself with the skin is very real. This is shown by the fact that it is possible to achieve positive patch tests with cement containing lower concentrations of chromium than would be effective in pure solutions. The experiments described in this work make it clear that it is possible, by treatment of the skin with suitable reagents, to modify its chromium uptake to a great extent. It would seem reasonable to regard the effects of the non-chromium cement constituents as analogous, in some degree, to some of the treatments described.

The conclusion which can be drawn from the blocking experiments would seem to be that there is no direct evidence that chromium is bound to the hydroxyl or amino groups of the collagen molecule or at the disulphide linkages. While direct evidence for binding by carboxyl groups has not been obtained, the indications are that these groups probably represent the active sites at which chromium is taken up. What is perhaps more important is that the production of dermatitis does not appear to be a quantitative function of the amount of metal bound to the skin and in this respect it resembles many other allergic conditions. It is perhaps possible to suggest that the findings in this work lend support to the concept that combination of even a minute portion of the skin collagen to chromium effects an immunological change in the protein molecule so completed and that the subsequent development of dermatitis is an antibody reaction to this modified protein.

SUMMARY.

Experiments showed that the binding of chromium to skin may be effected by many factors. Differences of pH have a very great influence on the uptake of chromium by the skin from potassium dichromate, a greater amount being taken up by solutions at lower pH values. This is interesting in view of the marked alkalinity of cement. There are also differences between the mode of binding of cationic trivalent chromium and that of the anionic hexavalent salt, which is in agreement with clinical findings.

Experiments to find the binding site of chromium in the collagen molecule were inconclusive. These experiments served to underline the complex nature of the binding process. It is possible that some of the other substances present in cement may have an important influence on binding chromium to skin. It seems probable that the carboxyl group of the collagen molecule is chiefly involved.

I wish to record my thanks to Dr. Martin Beare for suggesting this work and for his continued advice and help. Mr. D. Neill was very helpful with the biochemistry.

REFERENCES.

- ANDERSON, F. E. (1960) *Brit. J. Derm.*, **72**, 108.
 EPSTEIN, S. (1952) *Ann. Allergy*, **10**, 633.
 FLESCH, P. (1955) *J. Soc. cosmet. Chem.*, **6**, 161.
 ——— SATANOVE, A. and BROWN, C. S. (1955) *J. invest. Derm.*, **25**, 289.
 FRAENKEL-CONRAT, H. and OLCOTT, H. S. (1945) *J. biol. Chem.*, **161**, 259.
 GUSTAVSON, K. H. (1952) *Acta chem. scand.*, **6**, 1443.
 ——— (1956) *The Chemistry and Reactivity of Collagen*. New York: Academic Press Inc.
 HAXTHAUSEN, H. (1940) *Acta dermat.-venereol., Stockh.*, **21**, 158.
 ——— (1954) In *The Eczemas*, Ed. L. J. A. Loewenthal. Edinburgh: Livingstone.
 LANDSTEINER, K. and JACOBS, J. (1935) *J. exp. Med.*, **61**, 643.
 LILLIE, R. D. (1954) *Histopathologic Technic and Practical Histochemistry*. New York: The Blackiston Co. Inc.
 PEARSE, A. G. E. (1953) *Histochemistry, Theoretical and Applied*. London: J. and A. Churchill.
 PETERS, J. P. and VAN SLYKE, D. D. (1932) *Quantitative Clinical Chemistry*, Vol. II. Baltimore: Williams and Wilkins.
 SULZBERGER, M. B. and WITTEN, V. H. (1953) *Austr. J. Derm.*, **2**, 57.
 WELLS, G. C. (1956) *Brit. J. Derm.*, **68**, 237.
 WHITFIELD, A. (1921) *Lancet*, ii, 122.

LETTER FROM AZERBAIJAN.

BETWEEN the Black Sea and the Caspian, a high plateau ridged with barren red and green mountains constitutes the geographical area known as Azerbaijan. Like Gaul it is divided in three parts, one part in Turkey, a second in the U.S.S.R. and the third section occupies the north-west part of Iran. Originally known as the third Media or the Media of Atropatena, its history goes back deep into the roots of time and soldiers from this area were given an honoured position by Darius in his final attempt to stem the invasion of Alexander at Gau Gamela in 331 B.C. Unfortunately, history has never been kind to Azerbaijan and Alexander was neither the first nor the last of the invaders who occupied the country : Mark Antony came this way, Tamburlaine's army was only one of the Mongol hordes which irrputed into Azerbaijan, and Genghis Khan over-ran the area in 1221. As recently as 1948, the Government of Iran was compelled to ask for United Nations' help to persuade the Russians to withdraw their occupying forces and some Iranian newspapers still remind their readers of the invasion of Iran by the forces of Great Britain and Russia.

Military disasters are not the only troubles to have assailed this area and on at least two occasions in modern history, earthquakes have almost entirely destroyed the capital of the province. Until recently, therefore, Tabriz has shown an understandable reluctance to erect tall buildings. Even today the low flat-roofed style of house is the commonest to be seen and the general impression is of a widely spread city crouching at the foot of a semi-circle of red mountains.

In 1295, a successor of Genghis Khan, called Ghazan Khan, established the Il Khanid court at Tabriz and surrounded his own mausoleum with a monastery, a hospital, an observatory and a library, while his grand vazir Rashid-ad-din, who was also a practising physician, established a suburb of arts and sciences called the " Quarter of Rashid " which had 30,000 houses for artists, students, theologians, physicians and craftsmen. Unfortunately almost nothing of this now remains. In 1500, Shah Isma'il, founder of the Safavid dynasty, was crowned in Tabriz and later was compelled to defend his capital against the Sunni invaders led from Turkey by Suleiman the Magnificent, but continued threats from this quarter forced Isma'il to move his court away from Tabriz. Since that time, the rulers of Iran have shown little wish to move their capital to the north, as a consequence of which the gracious buildings of central and south Persia, with their tiled mosques and pooled courtyards, are missing from the scene. The only two buildings of historical interest to show the visitor are the Blue Mosque and the Arc.

The established religion in Iran is the Shi'a branch of the Moslem faith which has considerable divergences of belief from the Sunni branch which is most

adhered to in Arab countries, but although Azerbaijan has played little part in the development of this faith, two events of religious history have occurred. Zoroaster is reputed to have been born in Azerbaijan and at the other end of the scale of time, the latest Middle-Eastern prophet to found a religion, the Bab, initiator of the Baha'i faith, was executed in Tabriz by the established government in 1850.

The climate in Azerbaijan is rather more "continental" than most people in Europe imagine: the Royal Navy's tales of life in Abadan and the Persian Gulf have left the Englishman with the impression that the whole of Iran is almost unbearably hot for the majority of the year. Here in the North-west the weather is never extreme, in summer the temperature rarely rises to 100° F. and although the average temperature for the month of February this year was 20° F., in winter a bright sun warms the snow and a considerable number of people enjoy ski-ing in the local mountains.

Racially the population is mainly Turkish with an admixture of Mongolian and Iranian blood and there is a fairly large colony of Armenian and Assyrian Christians, left here by the receding tide of racial and religious intolerance. Azerbaijan has its own language, Turki, which has greater root connections with Turkish than Farsi but is an established language of its own with an individual grammar of considerable complexity. Turki was adopted as the official language under the Russian puppet government and since the return of Azerbaijan to Iran, the language has been officially discouraged and is neither taught in schools nor printed in the local newspapers. In spite of this background of historical and political turmoil, of schism and linguistic divergence, Tabriz has retained little sign of its turbulent past and is now a large city with almost a third of a million population, some wide streets, good hotels and cinemas. The increasing industrialization of Iran is still mainly on the small private-enterprise level, but Tabriz has two large match factories, a leather tannery, a brewery and innumerable carpet factories as well as the teeming productivity of the bazaar.

Fifteen years ago the University was founded with faculties of medicine and letters, since then faculties of agriculture and engineering have been opened and a large University site is now nearly ready for occupation. About 75 students are admitted each year to the medical faculty (in 1959 there were more than 1,000 applicants for the places) and the course is of 6 years' duration. The first year is devoted to the usual pre-medical sciences and the second and part of the third to anatomy and physiology. As the training is based on the French style of medical school, the students get little chance to work in the wards until the end of their fifth year when they are required to pass a mainly theoretical examination for admission to the compulsory interne year, in which they spend four months in a medical department, four months in the surgical wards and the rest as interne to a special department. At the end of the course

a thesis has to be presented on an original study incorporating clinical observation.

The students are taught dermatology during their fourth year; a course of two lectures a week has been established and the class is divided into four groups which attend for clinical teaching in the out-patients' department three mornings a week for two months. As is so common in English Universities, dermatology is the Cinderella of the school, and it was not until January 1959 that a full-time chair of dermatology was established in the University of Tabriz. At first housed in a large and rather gloomy old Iranian house, the department has recently moved to a more modern building which is shared with the E.N.T. department. A fairly large consulting room, treatment room, bathroom, two wards of four beds, pharmacy and patients' waiting room constitute the whole of the department which opens to receive patients at 8.00 every morning except Friday (here we work on Sundays). The majority of the patients come direct to the hospital and are not referred from the town doctors and each of them pay two rials (210 rials = £1) for a consultation. Those who cannot afford to pay are of course seen free. The pharmacy is supplied by the University with a number of useful drugs and simple lotions, creams and ointments are provided, as well as phenobarbitone, some antihistamines, chloroquine and a series of antibiotic and anti-tuberculous drugs. An attempt is made to ensure that these are only given to those who are unable to afford the cost of a prescription at an outside pharmacy.

Each patient when first seen is registered and notes are made and filed on every visit. A disease register has also been started and the following account of patients seen in Tabriz is derived from a study of the first 2,500 new cases recorded in the department (Table I). As in all dermatological clinics, the majority of cases fall into a very small number of diagnostic groups and the table shows that approximately 75% of the cases seen here can be placed into one of two dozen diagnoses. The eczema-dermatitis group is the most common, but to the Western dermatologist the most astonishing figure is that for favus. Nearly 11% of all the patients are suffering from active favus and this figure would be even higher if patients from the more remote villages could afford to attend for treatment, as it is estimated that nearly 40% of all children in the country districts are affected. In the past there has been a division of treatment. Radiotherapy has been used with some success, but the local radiographer, who is mainly self-taught, is well aware of the dangers of radiotherapy. Frequently a very low dose has been given because the fluctuations in the local electricity supply make it almost impossible to be certain of the actual dose that is emitted and in consequence, many children have been treated three or four times with no sign of dermatological damage, but also no sign of lasting improvement. Thallium acetate is used here considerably, in a dose calculated to be just less than 7 mg. per kilo body weight

TABLE I: *Skin Diseases of Most Frequent Incidence in Tabriz,
Based on an Analysis of 2,500 Cases.*

		%
Eczema—dermatitis group		24.28
Eczema (unclassified)	12.12%	
Neurodermatitis	5.20%	
Discoid eczema	3.20%	
Seborrhœic dermatitis	2.68%	
Atopic eczema	1.08%	
Pyogenic diseases		17.48
Impetigo	11.92%	
Folliculitis	2.84%	
Pyoderma	2.00%	
Ecthyma	0.72%	
Favus		10.68
Pruritus (all types)		4.68
Acne vulgaris		2.68
Pediculosis		2.76
Pediculosis corporis	1.56%	
Pediculosis capitis	1.20%	
Tuberculosis		2.34
Scrofuloderma	1.72%	
Lupus vulgaris	0.52%	
Papular urticaria		1.84
Pompholyx		1.61
Pityriasis versicolor		1.52
Urticaria		1.36
Psoriasis		1.20
Insect bites		1.20
Sun sensitivity		1.12
Warts (all types)		1.00

clothed, and associated, 14 days after administration, with manual epilation of the whole head. This treatment combined with the application of a modified Whitfield's ointment (containing 5% tincture of iodine) produces a considerable number of cures. Both these treatments will of course rapidly recede into history with the increased availability of griseofulvin. By the generous co-operation of Glaxo Laboratories, a large-scale investigation is at present being carried out which has had as startlingly successful results as could be wished. A report on this work will shortly be offered for publication.

The extremely high incidence of the pyococcal diseases is a reflection of the low standard of personal hygiene in the poorer members of the community; it is indeed unusual for most of the labouring classes to have soap in the house and the emphasis in the Koran on the need to wash with running water has effectively prevented a large number of the population from ever washing with warm water and soap. The frequent habit of swaddling, which the local Public Health Service and its home-visitors are trying to discourage, often precipitates a very severe infected intertrigo on the legs and groins and most of these cases are included in the pyoderma group. Tuberculosis is still appallingly common and although there were only thirteen cases of lupus vulgaris in the first 2,500 recorded cases, there were more than three times as many cases of scrofulo-

derma, mostly originating from infected cervical glands. Many of these cases are in surprisingly young children and it seems that those who manage to live past the age of five—about 40% do not—have a fairly high degree of acquired resistance.

Other than favus, the fungus infections are not a very great problem ; 1.52% of the cases had pityriasis versicolor and a number of children had microsporum and “ black dot ” ringworm which cannot be further identified at present owing to the absence of laboratory facilities. Of greater interest to the epidemiologically minded is the absence of tinea pedis, only one case of which has been seen. As the majority of the population used a “ modified Turkish ” type of public bath for their weekly wash, the assumption would seem to be that fungi which are attracted to the interdigital clefts are not at present resident in Azerbaijan, unless this mode of transmission is not as important as observers in England and America suggest.

To counteract this list of diseases with high incidence, it is pleasing to have to report that certain pests in British clinics are very rare. Only 25 cases in the surveyed number actually came to the hospital to complain about warts and only three of these were on the feet. Observation in other patients suggests that the small percentage is not because of a stoic toleration on the part of the children but is due to a genuinely low incidence in the population. There is a similar scarcity of patients with pruritus ani or pruritus vulvae, but this may be due to the highly developed sense of modesty felt by most Iranians ; it is however pleasing to note that nearly half the people who complain of generalized pruritus or urticaria are cured by the simple recognition and eradication of the particular intestinal parasite which is living with them at the time, the most common culprits being threadworms and round worms.

Also rare is housewife's or degreasing dermatitis which underlines the direct correlation with soap and water and raises a minor ethical problem—is it wise to recommend the increased use of soap for personal and domestic usage if the cost is a rapidly increasing rise in the incidence of alkaline dermatitis ? The population of Azerbaijan is also fortunate in that the cutaneous form of leishmaniasis is not seen in the north of Iran, only one patient having been treated, who probably acquired the disease when on holiday in the south.

In spite of the considerable amount of favus and a small amount of endemic leprosy, the routine work of the department is much the same as that of an English clinic. Smaller incidence of the stress diseases and the greater number of infective conditions allow the dermatologist to produce a pleasingly high cure rate, but this is only part of the satisfaction to be derived from working in a country where the hospitality of the university staff and the enthusiasm of the students make one feel warmly at home.

JOHN H. S. PETTIT.

ROYAL SOCIETY OF MEDICINE.

JOINT MEETING OF THE SECTIONS OF PAEDIATRICS AND DERMATOLOGY,
THE HOSPITAL FOR SICK CHILDREN, GREAT ORMOND STREET.

Presidents—Dr. CHARLES PINCKNEY and Professor J. T. INGRAM.

7 May 1959.

Two Cases of Phenylketonuria with Eczema.—Dr. BRIAN H. KIRMAN.

i. A boy, born 22.x.48.

Brother of second case (see below). No other siblings. Uncomplicated pregnancy and labour. Birth weight 7 lb. 5 oz. Retarded development; thought to be a cretin. History of *petit mal*. Walked at 7 years.

Admitted to Fountain Hospital on 18.v.50.

Examination.—Idiot; mental age 1 year. Wanders aimlessly. Spoon-fed. No fits since admission. Hair fair, eyes hazel. No characteristic physical signs. Test for phenylketonuria positive. History of eczema on face and forearms.

ii. A boy, born 4.xi.50.

Brother of first case (above). Uncomplicated pregnancy and labour. Birth weight 8 lb. 15 oz. Retarded development. Refused for adoption. History of eczema.

Admitted to Fountain Hospital on 22.v.53.

Examination.—Imbecile; mental age 2 years. Overactive. Feeds himself with spoon and cup. No history of fits. No characteristic physical signs. Hair blond, eyes blue. Test for phenylketonuria positive. Eczema on forearms.

Dr. C. E. WILLIAMS: People seem to think that all cases of phenylketonuria are necessarily mentally defective. That is not so. We had one boy who was subsequently proved to be of normal intelligence and the interesting point was that his hair pigment was not diminished. He had dark hair in contrast to the other cases who had little hair pigment and iris colour. He has had a lower blood phenylalanine than other phenylketonurics. He has had no treatment. He is now aged 15 and is reaching maturity.

The child was picked up by routine examination and was initially regarded a mentally defective child with a mild emotional disorder. He was admitted at the age of 4, and some 14 other cases were picked up at the age of 5 or 6. He was subsequently sent to an Educationally Sub-normal school where he was recently found to have a Stanford-Binet I.Q. of 94. The case has been reported by Cowie and Brandon (1958).

REFERENCE.

COWIE, V. and BRANDON, M. W. G. (1958) *J. ment. Def. Res.*, 2, 55.

Dr. I. B. SNEDDON: Is the eczema part of the genetic or the metabolic effect? If it is metabolic does it improve with dietary treatment?

Dr. C. E. WILLIAMS: From what I remember it does improve with dietetic treatment. We have not studied any families to find out if there are eczematous conditions in the family apart from phenylketonuria. Perhaps somebody working in this hospital can answer that.

Prof. T. B. FITZPATRICK (Boston, U.S.A.): Two interesting observations have been made in phenylketonuria: weakening of hair and eye colour and eczema. The mechanism of the former is quite well understood as a result of biochemical and clinical investigations. The diminution of melanin in phenylketonuria is related to the enormously increased phenylalanine content of the serum which inhibits melanogenesis. The inhibition of tyrosinase (the pigment-synthesizing enzyme) by phenylalanine is reversible and pigmentation of the hair returns when the phenylalanine concentration of the serum is reduced by a low phenylalanine diet. The inhibition can also be reversed by oral administration of large amounts of the melanin precursor, tyrosine, to patients with phenylketonuria. This restores the normal ratio of the inhibitor (phenylalanine) to the metabolite (tyrosine) and melanogenesis proceeds at a normal rate.

Little is known about the "eczema" that is said to be frequent in phenylketonuric children. Apparently this problem has not been brought to the attention of the dermatologist, since there

are no accurate descriptions of the clinical lesions or of their histopathology. One fact, however, seems fairly clear: the eczema in phenylketonuria disappears when the biochemical abnormality is abolished by maintenance on a low phenylalanine diet and returns again when the diet is stopped. This suggests that the biochemical abnormality may be related to the "eczema" occurring in phenylketonuria and it would be desirable to pin-point the metabolic pathway involved.

Juvenile Dermatitis Herpetiformis.—Dr. J. EVERALL (for Dr. R. T. BRAIN).

A boy aged 5.

History.—September 1956, onset of recurrent bullous vesicular eruption, mainly about the muco-cutaneous areas, with itching. Adopted child. Admitted to hospital in May 1957 with ? Stevens-Johnson syndrome. Lesions failed to respond to sulphapyridine but cleared rapidly with prednisone 5 mg. t.i.d. During the next twelve months recurrent attacks of bullous vesicular eruptions, despite prednisone therapy. Readmitted June 1958. Temporary improvement on dapsone 25 mg. daily but on sulphamethoxypyridazine (Lederkyn) 0.5 g. t.i.d., lesions immediately improved and cleared completely. Controlled with Lederkyn 0.25 g. daily. History of recurrent sore throats over last four months; readmitted for tonsillectomy. Congenital glaucoma treated in Moorfields Eye Hospital.

Comment.—Failure to respond to steroids, sulphapyridine and dapsone but controlled with sulphamethoxypyridazine.

There have been several reports of juvenile dermatitis herpetiformis being controlled with Lederkyn. This drug is not harmless. Two cases of dermatitis herpetiformis have been reported as having developed hepatitis after Lederkyn and one death has been reported after three weeks' treatment with Lederkyn.

THE PRESIDENT: I have seen one child's eruption go on into adult life, but most of them clear at puberty. I see no objection to the label. The reaction of a child before puberty and that of an adult may well be different.

Ehlers-Danlos Syndrome.—Dr. M. K. STRELLING (for Dr. R. T. BRAIN).

A girl aged 15.

History.—This only child was seen in 1950 with the complaint that on slight trauma her skin became torn or swellings appeared beneath it. Rubbing with a towel is painful. She subsequently developed migraine.

Examination.—The skin which has a velvety feel is hyperelastic, especially over the face and limbs. Hyperextensibility of joints is most noticeable in the fingers and toes. "Pseudo-tumours": loose folds of purplish skin over knees and elbows. Thin paper-like scars on the shins. Subcutaneous nodules have disappeared. Her father, who is an only child, also has the condition. The remainder of the family is unaffected.

Comments.—With the electron microscope, defects in the skin collagen have been shown and this may be the principal underlying pathology. The collagen fibrils do not seem to join properly to form fibres or fibre bundles, and as a result these can slide over one another more easily than in the normal.

A second comment is that of the nine cases seen at the Hospital for Sick Children, in the last sixteen years three have had skull skiagrams taken. All three showed a large bony defect in the region of the anterior fontanelle associated with multiple wormian bones, indicating defective ossification.

THE PRESIDENT: I think some of the cases of Miescher's elastoma have been associated with Ehlers-Danlos syndrome.

Dr. H. HABER: I know of several cases of Miescher's elastoma with an underlying Ehlers-Danlos syndrome.

Dr. M. FEIWEL: Common clinical features of Ehlers-Danlos syndrome, Miescher's elastoma and Marfan's syndrome (Haber, 1959) support a genetic mesodermal abnormality. Recently, Sjoerdsma, Davidson, Udenfried and Mitoma (1958) found excess hydroxyproline, an important constituent of collagen, excreted in urine of some patients with Marfan's syndrome.

REFERENCES.

HABER, H. (1959) *Brit. J. Derm.*, **71**, 85.

SJOERDSMA, A., DAVIDSON, J. D., UDENFRIED, S. and MITOMA, C. (1958) *Lancet*, ii, 994.

Eczema in Identical Twins.—Dr. W. FRAIN-BELL and Dr. P. KOBLENZER.

Two boys aged 14 months.

These identical twins developed an eczematous eruption at approximately the same time at the age of six weeks. In both it started behind the ears, and spread fairly extensively over the face, trunk and limbs and continued to fluctuate in severity until admitted to hospital on 22.iii.59 at the age of one year. In both the eczema had cleared by the time of discharge on 2.iv.59 but has relapsed somewhat since.

No other member of the family has suffered from asthma, eczema, or hay fever. First cousins once removed are also twins, otherwise the family history is non-contributory.

The eczematous reaction is still present in the skin of both children, one twin has more than the other.

Comment.—Eczema in identical twins is uncommon. It is interesting that the reaction started about the same time and has tended to fluctuate in severity and distribution and reaction to treatment in a similar way in both babies.

Postscript.—August 1959 : The eczema has cleared in both children. They have recently developed mild asthmatic symptoms in association with upper respiratory tract infection.

Case for Diagnosis (Macular Erythema and Chondritis).—Prof. E. G. L. BYWATERS (for Dr. I. ANDERSON).

A girl aged 7.

History.—Macular eruption noted on body the day after birth. Since then persistent rash, each lesion lasting about 24 hours. They come particularly on face and limbs, but also affect trunk. 1957, pain in right knees; limped. Thought to be tuberculous; treated with streptomycin, immobilization of knee and then a walking caliper. One year later, pain and swelling of left knee, treated by rest only. Referred to Rheumatism Research Unit at Taplow.

Examination.—Extensive maculo-papular rash. Pain on pressure over tibial spines with some limitation of movement of right knee joint.

Investigations.—E.S.R. 32 mm. in 1 hr. C.R.P. positive. D.A.T. 1:2. No L.E. cells found. Skiagrams of knees: osteochondritis of Osgood-Schlatter type affecting both tibial tubercles. Biopsy of left tibial tuberosity: normal cartilage containing several small areas of bone formation. No necrotic bone seen. Biopsy of skin: non-specific inflammatory changes.

Comment.—This child was shown by Dr. I. Anderson at the North of England Dermatological Society (*Brit. J. Derm.*, **71**, 231), where I do not think he received any suggestions as to the link between these two rare conditions or in fact what the two conditions were. We would be very grateful if anyone has any suggestions as to the nature of these changes and the link between them. I have shown the skiagrams to Dr. Campbell Golding who made the interesting suggestion that they might possibly be the changes associated with asymbolia, or with spina bifida occulta. I imagine this is a Charcot-like condition not of the joints but of the weight-bearing epiphyses. However, this patient has no radiological evidence of spina bifida, sensation and pain appreciation are normal, and we are at a loss to account for the changes seen.

Dr. G. C. WELLS: Is the rash identical with that seen in Still's disease?

Prof. BYWATERS: I think we would call it identical except that we have never seen a rash starting at birth and continuing for seven years. Many of the cases we have seen have a Still's

rash without arthritis, but it is usually accompanied by fever and the arthritis usually follows six months later, or something like that. Clinically it looks very much like the rash of Still's disease. We have biopsied it and the histological appearance is that of the rash in Still's disease, a sparse polymorph infiltration just beneath the epidermis.

THE PRESIDENT: Dr. Haber commented on the rarity of such rapid spontaneous disappearance without any evidence remaining behind and I have had the temerity to wonder if it were granuloma annulare, but I have not seen the pathology.

Dermatomyositis.—Dr. B. M. ANSELL.

A girl aged 10.

History.—In August 1957 she developed pain in the ankles, with difficulty in standing, which only lasted for a few days. Two months later movement of the right index finger was painful and over the following month all the fingers of both hands became painful and swollen with progressive loss of movement. Her general health deteriorated with much loss of weight, and in March 1958 painful lumps developed in the hands, around the ankles and behind the knees. There was a temporary improvement with physiotherapy and salicylates, but in August 1958 she developed severe pain in both legs, coldness of the feet and progressive difficulty in walking.

Examination.—When first seen in May 1958 the outstanding clinical finding was of nodules. They were present over the distal end of both radii, in the extensor tendons of both hands, in the region of the left metacarpophalangeal joints and around the lateral and medial malleoli of both ankles, and mid tarsal joints and along the tendons on the dorsum of both feet. No arthritis, but severe limitation of wrist, metacarpophalangeal, interphalangeal, ankle and metatarsophalangeal movement. By December 1958 she had developed a bluish discoloration of the face, her fingers were shiny and red and there were areas of atrophy on both elbows and the left knee. The skin was firmly bound over the muscles in the limbs and all the muscles were firm but not tender. There was residual thickening of both Achilles tendons, peroneal tendons and tendons in the hands.

Investigations.—Febrile (99–100° F.). E.S.R. 10 mm. in 1 hr. C.R.P. negative. W.B.C. 7100 per cu. mm., normal differential. D.A.T. 1:4. L.E. cells negative. Skiagram of joints normal. Biopsy of the peroneal tendon sheath showed some fibrin on the synovial lining with a few inflammatory cells. Some fibrinoid degeneration without extensive necrosis and some nodules of chronic inflammatory cells (lymphocytes and a few plasma cells). Extensive panniculitis.

Comment.—The general appearance suggests dermatomyositis, and the great loss of weight, general stiffness and pattern of the disease with normal E.S.R. and a negative D.A.T. of Rose-Waaler are fully compatible. An onset with extensive nodule formation is extremely unusual, and in older patients has occurred as a precursor of sclerodermatous changes.

On the whole the prognosis is good as regards life. In the last ten years we have had some thirteen children belonging to this group and in one or two cases the active phase has passed and left the skin looking very much like scleroderma. We have had one death from hypertensive encephalopathy while on steroid therapy, one from cerebro-vascular softening and two from bronchopneumonia, these three being before the advent of steroid therapy. We feel that the prognosis without steroid is probably about 50% mortality. With steroids we can get the acute cases into a more chronic state, sometimes with an initial dramatic response, but it is too soon to say whether it will prevent all the deformities which can occur.

The following cases were published in *Proc. R. Soc. Med.*, 52, 1029.

Acrodermatitis Enteropathica.—J. B. LYON, M.D., M.R.C.P.

Two Cases of Toxic Epidermal Necrolysis.—W. FRAIN-BELL, M.D., and P. KOBLENZER, M.R.C.P.Ed.

The following cases also were shown :

Scleroderma en Coup de Sabre with Cerebral Calcification.—Dr. S. D. V. WELLER.

(1) Hebra's Prurigo. (2) Epidermolysis Bullosa (Dowling type). (3) Two Cases of Tinea Capitis Treated with Griseofulvin.—Dr. R. H. MEARA.

? Von Recklinghausen's Disease. ? Tuberous Sclerosis. Dr. BRIAN H. KIRMAN.

(1) Pityriasis Rubra Pilaris. (2) Honeycomb Naevus. (3) Ectodermal Defect.—Dr. R. R. M. HARMAN (for Dr. T. R. BRAIN).

Pityriasis Lichenoides Chronica for Three Years in a Child Aged 6.—Dr. JOHN EVERALL (for Dr. R. T. BRAIN).

Hansen's Infection—Indeterminate Type.—Dr. JOHN EVERALL (for Dr. R. LIGHTWOOD and Dr. R. G. COCHRANE).

Adenoma Sebaceum.—Dr. K. K. STRELLING (for Dr. R. T. BRAIN).

(1) Linear Epidermal Naevus. (2) Lichen Sclerosus. (3) Epidermolysis Bullosa. (4) Lichen Sclerosus.—Dr. R. T. BRAIN.

Angioma.—Dr. P. KOBLENZER.

Discoid Lupus Erythematosus.—Dr. C. J. STEVENSON (for Dr. BRIAN F. RUSSELL).

Two Cases of Urticaria Pigmentosa in Identical Twins.—Dr. C. J. STEVENSON (for Dr. R. T. BRAIN).

Porokeratosis Mibelli.—Dr. A. P. NORMAN.

Ectodermal Defect.—Dr. H. J. WESTON (for Dr. G. H. NEWNS).

Dr. Martin Bodian gave a demonstration on the Histiocytic Reticulo-endothelioses, demonstrating the fundamental inter-relationship of Letterer-Siwe disease, Hand-Schüller-Christian syndrome and eosinophilic granuloma of bone.

BOOK REVIEW

A GERMAN TEXTBOOK.*

THE third volume of this handbook has now appeared. Like the second it consists of two parts. The first deals with dermatoses caused by external agents, peripheral vascular diseases, allergic manifestations, toxic damage to the skin and the eczema question.

Thermal and chemical damage to the skin is dealt with in great detail and the respective chapters contain much valuable information. The chapter on phyto-genic dermatoses gives much useful information on the chemical nature of plant irritants and a full list of plants known to be irritants arranged according to modern botanical classification. The chapter on drug eruptions is equally informative and includes a table of the commoner drugs responsible for skin manifestations showing the types of eruption they have been known to cause.

The second part contains chapters on diseases of the cutaneous appendages, including acne and rosecea, skin manifestations of diseases of other organs, skin diseases of pregnancy, the mineral metabolism of the skin, metabolic diseases and endocrine diseases. There are also very full accounts of leukaemia, Hodgkin's disease and mycosis fungoides. A special chapter is devoted to the discussion of pruritus which deals in great detail with the physiology of this symptom and puts forward interesting theories regarding its psychological explanation. Whereas treatment is often dealt with rather too briefly in other chapters there is a most detailed account of the treatment of pruritus. Most comprehensive lists of references follow each chapter and there is an index of authors as well as of subjects at the end of the second part.

W. G. T.

**Dermatologie und Venereologie*. H. A. GOTTRON and W. SCHÖNFELD, editors (1959). Stuttgart: Georg Thieme. Volume III, in two parts. Part 1, pp. 695, 232 illus. Price DM.165. Part 2, pp. 706, 317 illus. Price DM. 178.

SYMPOSIUM ON GRISEOFULVIN.

A Symposium on the Oral Treatment of Fungus Infections with Griseofulvin is to be held at the Royal Society of Medicine, London, W.1, on Friday and Saturday, 13 and 14 May 1960 with sessions on historical, clinical and pathological aspects. For particulars please apply to: The Secretary, Symposium on Fungus Infections, St. John's Hospital Dermatological Society, 5, Lisle Street, London, W.C.2.